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Topical Review

Septins: A Highly Conserved Family of Membrane-Associated GTPases with Functions in Cell Division and Beyond

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Introduction

Septins are members of a highly conserved protein family first identified in yeast and more recently found in a wide range of animal cells. Initially, septins were thought to function in controlling cytokinesis, as evidenced by their concentration at the mother-bud neck in budding yeast, and at the cleavage furrow in dividing animal cells. However, recent data suggest that they may function in a much broader array of contexts at sites where actin dynamics, cell surface organization and vesicle fusion processes are found. Several excellent reviews have been previously published which describe the identification of septins and their genetic properties in yeast (Sanders & Field, 1994; Chant, 1996; Cooper & Kiehart, 1996; Longtine et al., 1996). In this review I will primarily focus on more recent genetic and biochemical studies which hint at their functions, and provide some speculation about their possible roles in cytokinesis and other cellular processes particularly in animal cells.

The Discovery of Septins

Genetic approaches to study the mechanisms controlling yeast cell division began almost three decades ago and have led to the discovery of a great many genes whose products are necessary for the successful completion of the cell cycle (Hartwell, 1971; Nurse, Thuriaux & Nasmyth, 1976). Screens were carried out in yeast whose replication cycle was by budding (*Saccharomyces cerevisiae*) (Hartwell, 1971) or by fission (*Schizosaccharomyces pombe*) (Nurse et al., 1976), with the latter organism predicted to be more analogous to higher eukaryotes in its division mechanisms. Many of these genes, with homologues in both species, have been extensively characterized and shown to regulate a variety of crucial checkpoints in the cycle, while the precise functions of others still remain to be resolved. Mistakenly, one might dismiss many of the *S. cerevisiae* gene products as having roles specialized for the portion of the yeast cell cycle devoted to budding since a number of mutations were identified in these screens which altered bud morphology, location or ability to separate from the mother cell after growth was complete. However, one group of genes identified in which mutations caused bud growth defects encoded a family of proteins called **septins** (Sanders & Field, 1994). This new family of filamentous, membrane-associated proteins is conserved through evolution and required for a variety of cellular functions including cytokinesis.

In budding yeast, cell division proceeds by the selection of a bud site, where polarized secretion occurs to promote bud growth. At this point, a characteristic set of filaments is found at the neck between the mother cell and the growing bud. These filaments, with an apparent diameter of about 10 nm, form concentric rings around the neck in direct apposition to the cell membrane (Byers & Goetsch, 1976*a*). Targeted secretion continues to occur at the tip of the bud until the daughter cell is approximately two-thirds the size of the mother. At that time secretion becomes generalized over the entire surface of the daughter cell until the daughter and mother

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cell are approximately the same size (Byers, 1981). Recent studies have shown that the targeting of secretion coincides with the location of the multimolecular exocyst complex and that the location of the exocyst complex is controlled by Sec3p (Finger & Novick, 1997; Finger, Hughes & Novick, 1998). The exocyst complex moves from the tip to dispersed locations over the cell surface coincident with the change in exocytosis patterns. Finally, after the nuclei have divided, the secretory apparatus reorients to the mother-daughter neck and vesicle fusion occurs at the neck to separate the mother and daughter cells (Byers, 1981). The relationship between septin filament dissociation and vesicle fusion at the neck is not known.

Four complementing septin genes, CDC3, CDC10, CDC11 and CDC12, were originally described to give an indistinguishable phenotype with hyperpolarized buds, defects in cytokinesis and the abnormal deposition of cell wall chitin (Hartwell, 1971). Because the cells are not blocked in nuclear division or DNA replication, cells arrest with multiple nuclei. Cloning of these four genes revealed that each encoded a related protein of 30–60 kDa in size with a conserved GTP-binding domain near the N terminus (Haarer & Pringle, 1987; Ford & Pringle, 1991; Kim, Haarer & Pringle, 1991). Three of the four also had a coiled-coil motif near the C terminus although CDC10 lacks this feature. Antibodies raised against these proteins detect them at the mother-bud neck (Haarer & Pringle, 1987; Ford & Pringle, 1991; Kim et al., 1991) and, coupled with the fact that all four mutations caused disruption of the neck filaments (Byers & Goetsch, 1976*b*), this led to the suggestion that these proteins may co-assemble into filamentous structures. This family of proteins was given the name “septins” by J. Pringle and his colleagues due to their requisite role in the formation of the septum between the mother and bud cells during cytokinesis.

Two additional yeast septins, SPR3 and SPR28 have since been identified in yeast and appear to have a specific role in sporulation. SPR3 was identified by PCR using primers based on the sequences of the other known septins (Ozsarac et al., 1995; Fares, Goetsch & Pringle, 1996) while SPR28 was identified through homology searches on the completed yeast genome project (DeVirgilio, DeMarini & Pringle, 1996). Spr3p shares between 25–40% identity to each of the other septins while Spr28p shares 27–35% identity. SPR3 has been previously identified in a screen for genes involved in sporulation and its role in that process was supported by the observation that deletion of the gene reduces sporulation 3-fold, but only in certain genetic backgrounds. In contrast, deletion of CDC10 has no effect on sporulation indicating that not all septins are involved in this process. Immunofluorescence studies suggested that Spr3p colocalized with Cdc3p and Cdc11p at the leading edges of the membrane sacs involved in forming the spindle-pole bodies (Fares et al., 1996). Two hybrid studies using SPR28 as bait revealed interactions with itself and with N-termini of Cdc11p and Spr3p and with the entire Cdc3p protein (DeVirgilio et al., 1996). Like Spr3p, GFP-tagged versions of SPR28 similarly colocalize to the developing prospore walls and it was surprising, therefore, when it was observed that deletion of SPR28 had no effect on sporulation frequency. Furthermore, double mutants lacking both Spr3p and Spr28p sporulate normally. This has been interpreted to mean that neither of the sporulation-specific septins is absolutely required for sporulation and that there may be functional redundancy between sporulation and cytokinesis forms (DeVirgilio et al., 1996). Importantly, however, the two hybrid results suggest that septin filaments do not form solely through the coiled-coil domains at the C-termini of the proteins since the interactions are often only through the N-terminal portions. Since this is the region of the protein which binds GTP, GTP hydrolysis is likely to play an important role in filament assembly.

In contrast to budding yeast, animal cells divide by fission. During the mitotic stages of the cell cycle the cellular contents are divided in two main steps, karyokinesis and cytokinesis. The former is the process by which duplicated chromosomes, aligned on the cellular midplane, are pulled apart along microtubular spindles to ensure that each daughter cell receives an identical genomic complement. The alignment of the chromosomes specifies the plane in which the cells will divide, but the mechanisms controlling this are not known. Recent evidence suggests that the spindle structure is necessary for cleavage plane specification (Wheatley & Wang, 1996). In anaphase, after chromosomal segregation has taken place, cytokinesis begins with the formation of a contractile ring around the cleavage plane. The ring is known to contain actin, myosin and a number of other proteins and its constriction causes a furrowing of the underlying plasma membrane (Glotzer, 1997). By mechanisms that are not understood the two membranes are fused, dividing the two cells.

A general role for septins in cytokinesis in animal cells was first suggested when it was discovered that the *peanut* mutation in *Drosophila* was the result of a mutation in a septin homologue and that this mutation also disrupted cytokinesis (Neufeld & Rubin, 1994). In that organism, the phenotype of the *peanut* mutation is the development of multinucleated syncytia within imaginal discs, apparently due to failure in cytokinesis. Antibodies to the *peanut* protein revealed that in wild-type cells it localized to the contractile ring of mitotic cells in anaphase and concentrated at the cleavage furrow ingression during telophase. The observation that septins were required for cytokinesis in two very different cell division mechanisms, budding and fission, was remarkable and implied that these proteins are likely to carry out related processes in both systems (Sanders & Field, 1994). Sub-

Table. Homologies of the mammalian septin proteins

Name	Alignments (% identity)							Alternate Names	Expression Patterns	Chromosom. location
	1	2	3	4	5	6	7			
1) KIAA0202	—	77	42	41	41	39	42	—	Unknown	5q31
2) KIAA0128		—	41	44	40	38	39	—	Unknown	Xq25
3) CDCrel-1			—	76	60	61	53	PNUTL1	Predominantly brain	22q11.2
4) H5				—	61	62	53	—	Predominantly brain	17q23
5) Nedd5					—	53	57	Humdiff6	Ubiquitous	2q37
6) Diff6						—	46	Hypothetical 43.5K	Lymphocytes?	Unknown
7) HCDC10							—	—	Broad	7q36.1

Shown are the percent identities of pairwise comparisons between individual septin proteins through their overlapping regions. The numbers at the top correspond with those at the left. Alternative names of septin isoforms and their general expression patterns are also shown. Chromosome mapping information comes from references described in the text and from the NCBI Genemap.

sequent studies have led to the identification of two additional septin proteins in *Drosophila*, called Sep1 and Sep2 (Fares, Peifer & Pringle, 1995). Although mutations have not been identified in these proteins, antibodies against Sep1 demonstrate that, like *peanut*, it also concentrates at the cleavage furrow during mitosis.

cDNAs encoding seven distinct homologues of the septins have also been identified in mammals thus far, but very little is known regarding the structure or function of the proteins which they encode. Almost all have been identified through random cDNA cloning procedures or subtractive screens (Kato, 1990; Nottenberg, Gallatin & John, 1990; Tomooka & Noda, 1992; Nakasuru, Sodo & Nakamura, 1994; Nagase et al., 1995; Nagase et al., 1996; McKie et al., 1997; Zieger, Hashimoto & Ware, 1997). Unfortunately, the nomenclature of mammalian septins has become quite confusing because they were often named according to the protein to which they had most homology at the time they were identified, and not necessarily for their true orthologues. For example, HCDC10 was isolated through random cDNA sequencing studies and found to have homology with yeast septins and therefore named a human isoform of CDC10 (Nakasuru et al., 1994). However, unlike CDC10 of yeast, HCDC10 has a coiled-coil domain and is unlikely to be its true homologue. Similarly, the human cDNA humDiff6 was identified and named as a Diff6 homologue but this protein is actually the orthologue of mouse Nedd5.

Advances in the human genome project have led to the chromosomal mapping of most of the mammalian septins. Unfortunately, in most cases the location has provided few clues to their functions. HCDC10 maps to 7q36.1 near the XRCC2 gene involved in repair of X-ray induced damage to DNA (Tambini et al., 1997) but is not thought to contribute to this disorder. Human Nedd5 maps to 2q37 (Mori et al., 1996) but no diseases have been linked to this locus. CDCrel-1/PNUTL1 was identified as a gene located in a region of human chromosome 22q11.2 frequently deleted in DiGeorge syndrome (McKie et al., 1997). It has also been shown to be fused to the MLL gene in acute myeloid leukemia in twins with a t(11;22)(q23;q11.2) translocation (Megonigal et al., 1998), although the significance of this translocation in MLL activation remains to be determined. Additional septins may exist, and their identification remains an active area of research in many laboratories, using both sequence homologies and functional assays in their searches. In the Table I have summarized this information including the chromosomal locations and sequence identities for the human forms of each septin, with the exception of Diff6, for which human cDNAs exist in the dbEST database, but for which full length cDNA sequences have not been reported. In this case I compared the murine sequence with the human sequence for the other forms.

All mammalian septin isoforms share between 29 and 45% sequence identity with yeast septins and, as shown in Fig. 1, they share between 39 and 77% sequence identity with each other. Two pairs of septins stand out as sharing the highest sequence identity, specifically, KIAA0202 with KIAA0128, and H5 with CDCrel-1. Whether these represent functional homologues remains to be determined. Expression studies have shown that Nedd5 and HCDC10 are widely expressed and found in most tissues. H5 was identified as a brain-specific protein but we have found that it too is widely expressed but with highest expression in the brain (Xie et al., 1999). In studies from my lab we have also found that, contrary to the other septin types, CDCrel-1/PNUTL1 is almost exclusively expressed in the brain and in neuroendocrine tissues (Beites et al., 1999).

Genetic and Biochemical Properties of Septins

Genetic studies of septins and their interactions with other genes required for bud formation and cytokinesis have been extensively reviewed elsewhere (Chant, 1996; Longtine et al., 1996) and will not be covered here. In-

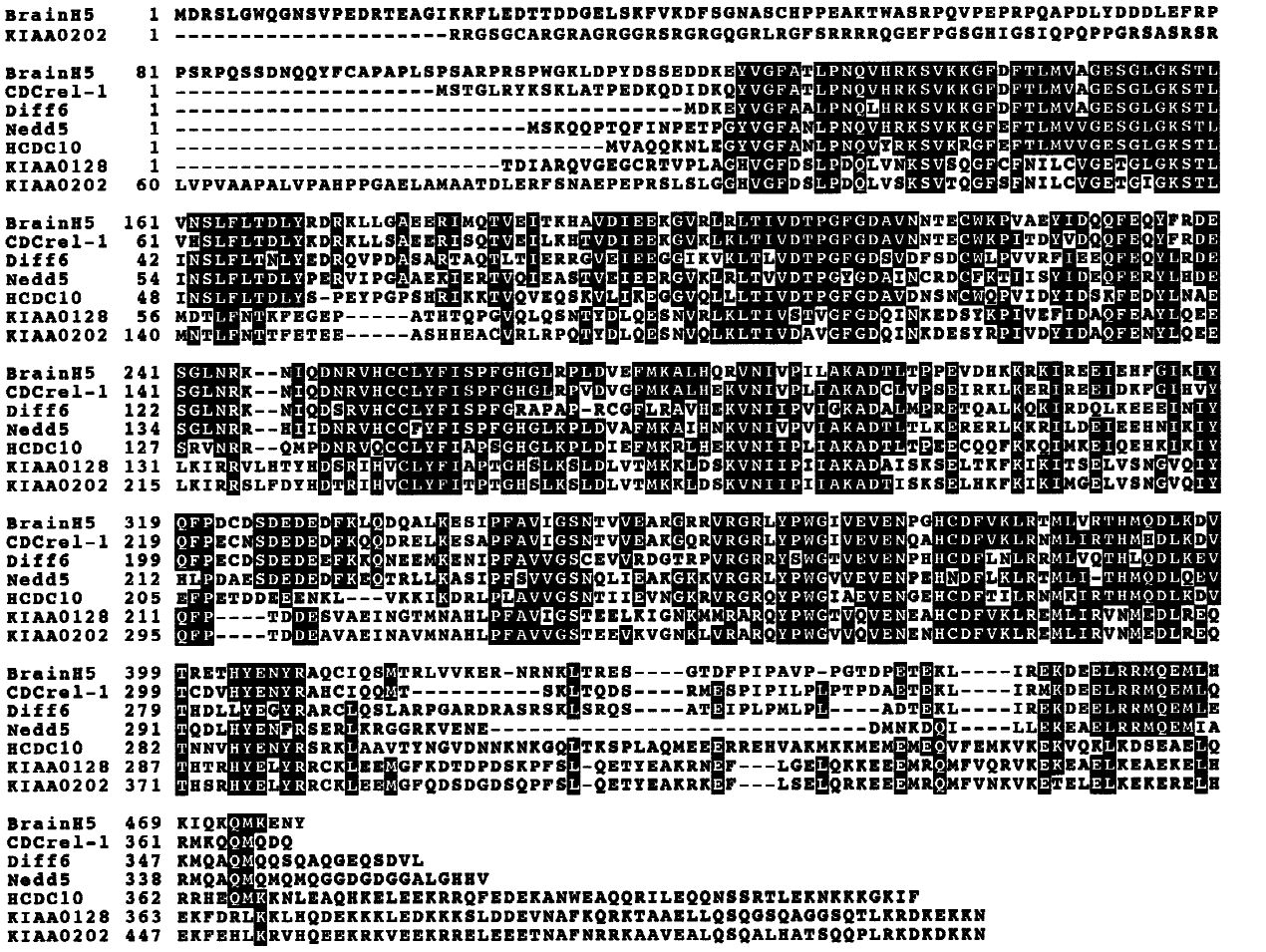

Fig. 1. Alignment of the mammalian septin proteins. Amino acid sequences of the human septins are shown with identical amino acids shown in outline. KIAA0128 and KIAA0202 are partial sequences lacking the amino termini. The sequence shown for Diff6 is derived from the mouse sequence since the human Diff6 has not been completely sequenced.

stead, I will describe some recent studies in yeast and animal cells that give insights into the nature of septin interactions with other proteins and each other which may begin to shed light on their functions.

Potential binding partners for the yeast septins have been identified through two-hybrid studies. In one case, the C-terminal portion of the protein Afr1p was found to interact with Cdc12p. Afr1p is induced by mating hormones, negatively regulates pheromone receptor signaling and is required for normal formation of the projection that becomes the site of fusion between mating yeast. However, the significance of this interaction is not clear because deletion of the Cdc12p binding domain did not alter Afr1p-mediated regulation of receptor signaling or mating projection formation. The interaction may only be required to facilitate the local action of the Afr1p protein (Giot & Konopka, 1997). However, Cdc12p is required for projection formation and this defect is not suppressed by overexpression of Afrp1, indicating that Cdc12p plays additional roles in this process aside from its association with Afr1p. Another direct binding target for septins is the protein Bni4p, a protein required for the normal deposition of chitin at the mother bud neck. Bni4p binds the septin Cdc10p and coordinates the location of the chitin synthase III gene activator Chs4p which in turn maintains the location of Chs3p, the catalytic subunit of chitin synthase III (DeMarini et al., 1997). This observation suggests that septins can function to regulate the organization of membrane proteins on the cell surface. The fact that different septins may bind different proteins indicates that septin filaments may be able to act as multicomponent adaptors to bring particular proteins into close proximity.

In *Drosophila*, biochemical evidence has been obtained which shows that septins can assemble into multimeric complexes capable of co-immunoprecipitation (Field et al., 1996). These complexes appear to be mixtures of each septin and electron microscopic analysis of immunoisolated complexes suggests that they form filaments from repeats of unitary complexes which appear to

be composed of heterotrimers of homodimers. *Drosophila* septin complex units are approximately 25 nm long and about 7–8 nm in diameter. Complexes are also associated with guanine nucleotides in a GDP:GTP ratio of 2.6. Filament aggregation in lateral cable-like bundles was seen if septins were maintained at high concentrations or purified from buffers containing 1.5% polyethylene glycol, suggesting that polymerization may occur either linearly, through lateral association of units, or both. GTP binding and exchange were measured in the immunoisolated complexes and it was found that the exchange rate was quite slow while the hydrolysis occurred quickly (Field et al., 1996). It is not known if additional proteins are required to regulate the binding and exchange of GTP, or to control its hydrolysis, but based on the homologies of the GTP-binding motifs with those of the ras GTPase superfamily, this possibility seems likely.

Evidence for the role of GTP hydrolysis in septin filaments assembly has come recently from the studies of Noda and colleagues (Kinoshita et al., 1997) who examined the location and functional importance of the mammalian septin Nedd5. They show that in resting fibroblasts Nedd5 colocalizes with actin stress fibers and concentrates at the cleavage furrow in telophase cells. Treatment of cells with cytochalasin D, which blocks actin filament formation, also results in the disruption of septin filaments. Furthermore, they show that GTP hydrolysis is required for Nedd5 to form filaments. By introducing mutations into the GTP binding domain analogous to those which prevent GTP binding or stabilize the GTP-bound state in ras, they were able to establish that mutant septins acted dominantly to interfere with septin filament formation and stability. The mutated Nedd5 proteins were microinjected into fibroblasts ans shown to disrupt endogenous Nedd5 filaments, the same effect they obtained when they injected antibodies against Nedd5 or GTPγS. Taken together, they interpreted these results as showing that GTP hydrolysis is necessary for filament assembly and the proteins unable to bind and hydrolyze GTP prevented this process from occurring (Kinoshita et al., 1997). Injected cells also had a high frequency of multinucleation, indicating that in the absence of Nedd5 filaments the cells were unable to complete cytokinesis. However, the septin mutants and antibodies were without any effect on actin stress fibers or the actin filaments associated with the cleavage furrow. It remains unclear how septins associate with actin filaments, and it is not known what role they play in cytokinesis.

We have produced antibodies to several of the mammalian septins and found that they colocalize to the cleavage furrow of mitotic cells. However, in resting fibroblasts, individual septins appear to be differentially localized. Nedd5 associates with portions of the actin stress fibers, particularly in the central portion of the cell where they localize under the nucleus. In contrast, H5 and HCDC10 both appear to completely mimic the pattern obtained with actin, including accumulations at membrane borders and in ruffles (Xie et al., 1999). Current studies are underway to determine if different septin proteins respond differently to growth factor stimulation. In any case, immunocytochemical and immunoprecipitation studies suggest that septins do not always colocalize within cells and indicate that they may form more than one type of filament.

We have also recently observed that septins contain motifs capable of binding to phosphatidylinositol-bisphosphate (PIP2) in vitro and in vivo (J. Zhang et al., *manuscript submitted*). Adjacent to the GTP-binding motif of several septins is a lysine-rich motif found in many proteins displaying PIP2 binding properties. Since GTP hydrolysis is implicated in filament assembly, the proximity of the PIP2 binding site to the GTPase domain could permit spatial and temporal control of filament growth and membrane attachment through PIP2 signaling cascades.

Septins and Exocytosis: New Functions of Septins in Mammalian Cells?

The expression patterns of mammalian septins indicate that different cell types must have different ratios if individual septin proteins and septins therefore cannot always associate in filamentous complexes with stoichiometric ratios. Individual cell types must make different types of septin filaments and, if each septin protein has different functions, filaments from different cell types would therefore have unique properties. Much additional research is needed to determine the mechanisms controlling septin filament assembly, the organization of individual septins within filaments, and the role of different compositions on filament function. Remarkably, the highest levels of septin expression appears to occur in the brain, a predominantly nonmitotic tissue. This must indicate that at least some of the functions mediated by septins have nothing to do with cytokinesis and are required in neurons.

A surprising observation about the presence of septin filaments in the brain was presented in a recent paper from the Richard Scheller's group (Hsu et al., 1998). In that study they found that septin proteins associated with the multimolecular rSEC6/rSEC8 complex, the mammalian equivalent of the yeast exocyst complex discussed above, during its purification. The purified septins were found in filamentous structures and displayed average diameters of 8.25 nm and lengths in repeats of 25 nm, similar to that observed in *Drosophila.* At least 5 bands between 44 and 52 kiloDaltons could be detected in immunoisolated rSEC6/rSEC8 complexes and amino

acid sequence analysis revealed that they were members of the septin family. However, due to the high degree of sequence identity between septin isoforms, identification of individual species remained unclear. Nonetheless, the association of septins with the rSEC6/rSEC8 complex provides compelling evidence to suggest that septins may participate in vesicle traffic or membrane protein localization.

In support of this observation, recent evidence from my laboratory also supports a link between septins and vesicles (Beites et al., 1999). We have observed that the septin CDCrel-1, is predominantly expressed in the brain. Unexpectedly, it is associated with membranes in the brain (despite the lack of membrane domains) and co-purifies with synaptic vesicles. Immunoprecipitation experiments have shown that it co-precipitates with the protein syntaxin with which it binds directly in vitro. Syntaxin is a component of the machinery thought to be responsible for regulating the fusion of vesicles with their target membranes and is a central component of the SNARE hypothesis. By deletion analysis, we have found that the CDCrel-1 binding site maps to the site in syntaxin to which the other SNARE proteins, VAMP and SNAP-25 bind to form the docking/fusion complex, suggesting the possibility that CDCrel-1 may participate in regulated exocytosis. The presence of GTP-binding domains also suggested that this nucleotide might participate in regulating its role in this process. To test these hypotheses we transfected secretory cells and measured the effect on exocytosis. To examine the role of the GTP-binding domain in this protein we constructed the same dominant-negative mutation described above for Nedd5 in CDCrel-1. HIT-T15 cells were transfected with wild-type or mutant CDCrel-1 and the response of the cells to depolarization by high extracellular potassium was measured as a determinant of evoked secretion. Transfection of wild-type CDCrel-1 into HIT-T15 insulinoma cells caused a significant decrease in evoked secretion. Dramatically, transfection of dominant-negative mutants of this protein significantly increased secretion although it had no effect on syntaxin binding (Beites et al., 1999). Since septins can bind to syntaxin, a SNARE protein found on both vesicles and plasma membranes, and form filaments with other septins, then their effect on secretion may be the result of their ability to tether the vesicles to the membrane and to each other, thereby sequestering them and modulating exocytosis. The dominant-negative mutants which disrupt filaments would release the vesicles from their endogenous tethers and facilitate exocytosis. This is an exciting possibility since unidentified filamentous structures have been detected in deep etch micrographs of nerve terminals for many years (Landis et al., 1988; Hirokawa et al., 1989). The role of septins in secretion may not be solely negative, but rather to maintain vesicle concentrations near their site of release to optimize spatial and temporal control. Such a filamentous GTPase tethering the vesicle to the membrane is exactly analogous to the scaffolding proteins hypothesized by Monck and Fernandez (1994).

Vesicle Trafficking: A Common Theme?

The association of septins with syntaxin and vesicles raises the possibility that the role of septins in cytokinesis may also involve vesicle targeting and fusion and such a link can be inferred from a variety of published observations. For example, in *Drosophila*, embryogenesis proceeds first by nuclear divisions and then by cellularization, during which membranes are created between nuclei via vesicle fusion events. The septin Peanut has been shown to localize to the leading edge of the membrane invaginations that partition the nuclei (Neufeld & Rubin, 1994), implying that septins assist in some aspect of the alignment or transport of vesicles during this form of cell division. Interestingly, syntaxin was also shown to localize to this site (Burgess, Deitcher & Schwarz, 1997), further supporting our link between these two classes of proteins. As stated above, cytokinesis in budding yeast also appears to require a vesicle fusion step to mediate the fission of the plasma membranes between the mother and daughter cells (Byers, 1981) at the site septins reside throughout bud growth, and this step fails in septin mutants. Septins are also required for sporulation at sites where vesicle fusions occur to form the membrane sacs associated with spindle pole formation (DeVirgilio et al., 1996; Ozsarac et al., 1995; Fares et al., 1996). Although the final steps of cytokinesis in mammalian cells are not known, it will be of great interest to determine if the requisite role of septins in this process involves the directed sequestration and fusion of vesicles at the cleavage furrow.

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References

Beites, C., Xie, H., Bowser, R., Trimble, W. 1999. The septin CDCrel-1 binds syntaxin and inhibits exocytosis. *Nature Neurosci.* (*in press*)

Burgess, R., Deitcher, D., Schwarz, T. 1997. The synaptic protein syntaxin1 is required for cellularization of Drosophila embryos. *J. Cell Biol.* **138:**861–875

Byers, B. 1981. Cytology of the yeast life cycle. *In:* The Molecular Biology of the Yeast Saccharomyces, Life Cycle and Inheritance. J. Strathern, E. Jones, and J. Broach, editors. pp. 59–96. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY

Byers, B., Goetsch, L. 1976*a*. A highly ordered ring of membrane-associated filaments in budding yeast. *J. Cell Biol.* **69:**717–721

Byers, B., Goetsch, L. 1976*b*. Loss of the filamentous ring in cytokinesis-defective mutants of budding yeast. *J. Cell Biol.* **70:**35

Chant, J. 1996. Septin scaffolds and cleavage planes in saccharomyces. *Cell* **84:**187–190

Cooper, J.A., Kiehart, D.P. 1996. Septins may form a ubiquitous family of cytoskeletal filaments. *J. Cell Biol.* **134:**1345–1348

DeMarini, D.J., Adams, A.E.M., Fares, H., Vergilio, C.D., Valle, G., Chuang, J.S., Pringle, J.R. 1997. A septin-based hierarchy of proteins required for localized deposition of chitin in the Saccharomyces cerevisiae cell wall. *J. Cell Biol.* **139:**75–93

DeVirgilio, C., DeMarini, D.J., Pringle, J.R. 1996. SPR28, a sixth member of the septin gene family in Saccharomyces cerevisiae that is expressed specifically in sporulating cells. *Microbiology* **142:**2897–2905

Fares, H., Goetsch, L., Pringle, J.R. 1996. Identification of a developmentally regulated septin and involvement of the septins in spore formation in Saccharomyces cerevisiae. *J. Cell Biol.* **132:**399–411

Fares, H., Peifer, M., Pringle, J.R. 1995. Localization and possible functions of Drosophila Septins. *Mol. Biol. Cell* **6:**1843–1859

Field, C.M., Al-Awar, O., Rosenblatt, J., Wong, M.L., Alberts, B., Mitchison, T.J. 1996. A purified Drosophila septin complex forms filaments and exhibits GTPase activity. *J. Cell Biol.* **133:**605–616

Finger, F., Hughes, T., Novick, P. 1998. Sec3p is a spatial landmark for polarized secretion in budding yeast. *Cell* **92:**559–571

Finger, F.P., Novick, P. 1997. Sec3p is involved in secretion and morphogenesis in Saccharomyes cerevisiae. *Mol. Biol. Cell* **8:**647–662

Ford, S.K., Pringle, J.R. 1991. Cellular morphogenesis in the Saccharomyces cerevisiae cell cycle: localization of the CDC11 gene product and the timing of events at the budding site. *Devel. Genet.* **12:**281–292

Giot, L., Konopka, J.B. 1997. Functional analysis of the interaction between Afr1p and the Cdc12p septin, two proteins involved in pheromone-induced morphogenesis. *Mol. Biol. Cell* **8:**987–998

Glotzer, M. 1997. The mechanism and control of cytokinesis. *Curr. Opin. Cell Biol.* **9:**815–823

Haarer, B.K., Pringle, J.R. 1987. Immunofluorescence localization of the Saccharomyces cerevisiae CDC12 gene product to the vicinity of the 10-nm filaments in the mother-bud neck. *Mol. Cell. Biol.* **7:**3678–3687

Hartwell, L. 1971. Genetic control of the cell division cycle in yeast. IV. Genes controlling bud emergence and cytokinesis. *Exp. Cell Res.* **69:**265–276

Hirokawa, N., Sobue, K., Kanda, K., Harada, A., Yorifuji, H. 1989. The cytoskeletal architecture of the presynaptic terminal and molecular structure of synapsin 1. *J. Cell Biol.* **108:**111–126

Hsu, S.-C., Hazuka, C., Roth, R., Foletti, D., Heuser, J., Scheller, R. 1998. Subunit Composition, protein interactions and structures of the mammalian brain sec6/8 complex and septin filaments. *Neuron* **20:**1111–1122

Kato, K. 1990. A collection of cDNA clones with specific expression patterns in mouse brain. *Eur. J. Neurosci.* **2:**704–711

Kim, H.B., Haarer, B.K., Pringle, J.R. 1991. Cellular morphogenesis in the Saccharomyces cerevisiae cell cycle: localization of the CDC3 gene product and the timing of events at the budding site. *J. Cell Biol.* **112:**535–544

Kinoshita, M., Kumar, S., Mizoguchi, A., Ide, C., Kinoshita, A., Haraguchi, T., Hiraoka, Y., Noda, M. 1997. Nedd5, a mammalian septin, is a novel cytoskeletal component interacting with actin-based structures. *Genes Devel.* **11:**1535–1547

Kumar, S., Tomooka, Y., Noda, M. 1992. Identification of a set of genes with developmentally down-regulated expression in the mouse brain. *Biochem. Biophys. Res. Comm.* **185:**1155–1161

Landis, D., Hall, A., Weinstein, L., Reese, T. 1988. The organization of cytoplasm at the presynaptic active zone of a central nervous system synapse. *Neuron* **1:**201–209

Longtine, M.S., DeMarini, D.J., Valencik, M.L., Al-Awar, O.S., Fares, H., Virgilio, C.D., Pringle, J.R. 1996. The Septins: roles in cytokinesis and other processes. *Curr. Opin. Cell Biol.* **8:**106–119

McKie, J.M., Sutherland, H.F., Harvey, E., Kim, U.-J., Scambler, P.J. 1997. A human gene similar to Drosophila melanogaster peanut maps to the DiGeorge syndrome region of 22q11. *Hum. Genet.* **101:**6–12

Megonigal, M., Rappaport, E., Jones, D., Williams, T., Lovett, B., Kelly, K., Lerou, P., Moulton, T., Budarf, M., Felix, C. 1998. t(11;22)(q23;11.2) in acute myeloid leukemia of infant twins fuses MLL with hCDCrel, a cell division cycle gene in the genomic region of deletion in DiGeorge and velocardiofacial syndromes. *Proc. Natl. Acad. Sci. USA* **95:**6413–6418

Monck J., Fernandez, J. 1994. The exocytic fusion pore and neurotransmitter release. *Neuron* **12:**707–716

Mori, T., Miura, K., Fujiwara, T., Shin, S., Inazawa, J., Nakamura, Y. 1996. Isolation and mapping of a human gene (DIFF6) homologous to yeast CDC3, CDC10, CDC11, and CDC12, and mouse Diff6. *Cytogenet. Cell Genet.* **73:**224–227

Nagase, T., Seki, N., Ishikawa, K., Ohira, M., Kawabayashi, Y., Ohara, O., Tanaka, A., Kotani, H., Miyajima, N., Nomura, N. 1996. Prediction of the coding sequences of unidentified human genes. VI. The coding sequences of 80 new genes (KIAA0201-KIAA0280) deduced by analysis of cDNA clones from the human cell line KG-1 and brain. *DNA Res. 3:*321–329

Nagase, T., Seki, N., Tanaka, A., Ishikawa, K., Nomura, N. 1995. Prediction of the coding sequences of unidentified human genes. IV. The coding sequences of 40 new genes (KIAA0121-KIAA0160) deduced by analysis of cDNA clones from the human cell line KG-1. *DNA Res.* **2:**167–174

Nakasuru, S., Sudo, K., Nakamura, Y. 1994. Molecular cloning of a novel human cDNA homologous to CDC10 in Saccharomyces cerevisiae. *Biochem. Biophys. Res. Comm.* **202:**82–87

Neufeld, T.P., Rubin, G.M. 1994. The Drosophila peanut gene is required for cytokinesis and encodes a protein similar to yeast putative bud neck filament proteins. *Cell* **77:**371–379

Nottenberg, C., Gallatin, W.M., John, T.S. 1990. Lymphocyte HEV adhesion variants differ in the expression of multiple gene sequences. *Gene* **95:**279–284

Nurse, P., Thuriaux, P., Nasmyth, K. 1976. Genetic control of the cell divison cycle in the fission yeast Schizosaccharomyces pombe. *Mol. Gen. Genet.* **146:**167–78

Ozsarac, N., Bhattacharyya, M., Dawes, I.W., Clancy, M.J. 1995. SPR3 gene encodes a sporulation-specific homologue of the yeast CDC3/10/11/12 family of bud neck microfilament genes and is regulated by ABF1. *Gene* **164:**157–162

Sanders, S.L., Field, C.M. 1994. Septins in common? *Current Biology* **4:**907–910

Tambini, C.E., George, A.M., Rommens, J.M., Tsui, L.-C., Scherer, S.W., Thacker, J. 1997. The XRCC2 DNA repair gene: Identification of a positional candidate. *Genomics* **41:**84–92

Wheatley, S., Wang, Y.-I. 1996. Midzone microtubule bundles are continuously required for cytokinesis in cultured epithelial cells. *J. Cell Biol.* **135:**981–989

Xie, H., Howard, J., Surka, M., Trimble, W. 1999. Characterization of the mammalian septin H5: Distinct properties of cytoskeletal and membrane association from other mammalian septins. *Cell Motil. Cytoskel.* (*in press*)

Zieger, B., Hashimoto, Y., Ware, J. 1997. Alternative expression of platelet glycoprotein Ibbeta mRNA from an adjacent 5′ gene with an imperfect polyadenylation signal sequence. *J. Clin. Invest.* **99:**520–525